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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/778,672	02/07/2001	Hsu Ching-Hsaing	12774-002001	4367

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EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 12/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/778,672	CHING-HSAING ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-33,35-39 and 41-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-33,35-39 and 41-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 February 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/12/03 has been entered.

Claims 24-33, 35-39, 41-49 are pending and under current examination.

Drawings

New corrected drawings are required in this application because informal drawings containing handwritten legends are in the file. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Claim Objections

Claim 35 is objected to because it depends from a canceled claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 26, 27, and 46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 26 is vague and indefinite because it is incomplete, a verb is missing in the sentence. The meaning of the claim is unclear in the context of the claim, thus the metes and bounds of the claim could not be determined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The Declaration under 37 CFR § 1.132 of Dr. Hsu filed 7/11/2003 has been considered. The rejection under this section has been modified in view of the amendment, the Declaration, and Response. Applicants' arguments would be addressed to the extent that they apply to the current rejection.

Claims 24-33, 35-39, and 41-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Hsu et al* (US 5,958,891) and *Janeway Jr.* (Immunobiology, 1999), in view of *Pouwels et al* (Intl J Food Microbial 1998;41:155-67) and *Medaglini et al* (PNAS 1995;92:6868-72, IDS/AI).

Hsu et al teach a method of suppressing allergen-specific IgE production in a subject comprising administering to the subject a recombinant plasmid (comprising a CMV promoter operably linked to a sequence encoding an allergen and administered via intramuscular, intranasal, and intratracheal routes (abstract), preferably the allergen is dust mite *Dermatophagoides pteronyssinus* Der p5 allergen via intramuscular injection (paragraph bridging columns 3 & 4), wherein upon subsequent challenge with allergen Der p5 i.p. or i.h., a 90% reduction of IgE was observed in the treated group compared to the controls (column 8, lines 24-38), wherein the subject is a human subject (claims 3 and 8). *Hsu et al* also teach that the vector administration could suppress allergen-induced airway inflammation and bronchopulmonary congestion upon aerosol Der p5 exposure (paragraph bridging columns 9-10) and the suppression was concurrent with a T cell response and production of **IgG** (1st paragraph under Detailed

description). *Hsu et al* do not teach using a Gram-positive bacterium as the expression vehicle.

Janeway Jr. teach in the context of treating allergy (desensitization) and inhibiting IgE production, "IN DESENSITIZATION, THE AIM IS TO SHIFT THE ANTIBODY RESPONSE AWAY FROM AN IGE-DOMINATED RESPONSE (suppressing IgE) TOWARDS ONE DOMINATED BY IGG (enhancing IgG production), WHICH CAN PREVENT THE ALLERGEN FROM ACTIVATING IGE-MEDIATED EFFECTOR PATHWAYS" (12-15, annotation added) or "AN ALTERNATIVE, AND STILL EXPERIMENTAL, APPROACH TO DESENSITIZATION IS VACCINATION WITH PEPTIDES DERIVED FROM COMMON ALLERGENS. THIS PROCEDURE INDUCES T-CELL ANERGY (SEE SECTION 8-11), WHICH IS ASSOCIATED WITH MULTIPLE CHANGES IN THE T-CELL PHENOTYPE, INCLUDING DOWNREGULATION OF CYTOKINE PRODUCTION AND REDUCED EXPRESSION OF THE CD3:T-CELL RECEPTOR COMPLEX. IGE-MEDIATED RESPONSES ARE NOT INDUCED BY THE PEPTIDES BECAUSE IGE, IN CONTRAST TO T CELLS, CAN ONLY RECOGNIZE THE INTACT ANTIGEN". *Janeway Jr.* does not discuss the detail with respect to how the antigenic peptide is being delivered.

Pouwels et al teach that lactic acid bacteria is a family of non-pathogenic, Gram-positive bacterium that could be genetically modified for use as antigen delivery vehicles for oral immunization purpose (See e.g. the abstract). They teach a method comprising orally administering to a subject a strain of lactic acid bacteria (LAB) that comprises a nucleotide sequence encoding a heterologous protein antigen operably linked to a promoter functional in the LAB (§ 7), preferably the promoter is IdhL promoter (fig. 4), wherein the antigenic protein would be expressed intracellularly or surface-bound in the subject (§ 7.1) in a sufficient amount to stimulate the host immune system (§ 7.2), not only locally but also systemically (§ 4.4). *Pouwels et al* teach that LAB can serve as a

general DNA vaccine carrier for several reasons, a). They can be delivered *orally*, which can be carried out on a large scale and relatively inexpensive as compared to the parenteral route; but more importantly, many antigens enter the body via the mucosal surfaces, thus, the gastrointestinal system is naturally the largest first line of defense in the body (§ 2); b). LABs are involved in food processing, manufacture of dairy products (including yogurt) since for ever, thus are *safe* for animals, they are resistant to the harsh environment of GI, and some strains have additional health-promoting activities (§ 3); c). LABs are low in immunogenecity, but can non-specifically increase antigen-specific immune response (§ 4.4). *Pouwels et al* go on to teach that recombinant LAB allows efficient expression of heterologous antigen and presenting antigens in different ways to the immune system, which offers opportunities to further explore the potential of these food bacteria as vaccine vehicles. *Pouwels et al* do not particularly teach using the system for expressing allergens for desensitization.

Medaglini et al teach another non-pathogenic Gram-positive commensal bacteria system *Streptococcus gordonii*, which allow stable expression of a wide range of peptide antigens on its surface (abstract and right column on page 6870). The exemplified embodiment is transforming *Streptococcus gordonii* with a recombinant plasmid pSMB7 expressing an allergen (hornet venom M6 protein) on the surface of the *S. gordonii*. They administered the recombinant bacterial construct to mice orally and intranasally, and successfully expressed the allergen while the Gram-positive, non-pathogenic bacterium is in the mice. They teach that the allergens or other antigens could be expressed sufficiently to induce local and systemic immune response while in

a subject. They observed significant IgG immune response to the specific allergen. They teach the system is suitable for use as a carrier for wide range of antigens (Discussion). *Medaglini et al* do not measure IgE nor express a dust mite allergen.

Evidently, at the time of the invention, it is well known in the art that IgE production could be specifically suppressed by delivering an allergen to a mammal as taught by *Hsu et al and Janeway Jr.* It is also well known in the art that both an eukaryotic expression carrier and a prokaryotic expression carrier could be used for delivering an antigen to a mammal for vaccine purposes, and LAB or other oral commensal bacteria offer an alternative to the parenteral plasmid administration in DNA vaccination, providing a safe carrier and a non-specific adjuvant as taught by *Pouwels et al.* It is additionally well known that it is practical to express an allergen in such a non-pathogenic, Gram-positive bacteria system and induce a systemic IgG antibody response as taught by *Medaglini et al.* It is known as well that IgE production could be suppressed by inducing an IgG response as taught by *Janeway Jr.*

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify and combine the methods taught by *Hsu et al, Janeway, Jr., Pouwels et al,* and *Medaglini et al* by expressing the Der p5 allergen using the plasmid pSMB7 or alike such as those taught by *Pouwels et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention for the multiple beneficial effects of LAB as taught by *Pouwels et al*, as well as adopting the strategy as taught by *Janeway, Jr.* shifting the antibody response away from an IgE-dominated response toward one dominated by

IgG. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Declaration of Dr. Hsu and Arguments

The following paragraphs will address each issue discussed in the Declaration and accordingly discussed in the Remarks filed 9/12/03.

Eukaryotic and Prokaryotic Expression.

Applicants emphasized the differences in antigen expression between the bacterial vaccine carrier (external to the mammalian cells of the mucosa, taught by *Medaglini et al*) and the plasmid (inside of a mammalian cell, taught by Hsu et al), and concluded that there is no motivation to combine references.

The arguments have been fully considered but they are not persuasive for reasons detailed above and following.

It is acknowledged that it is a well-known fact that the eukaryotic and prokaryotic expressions are vastly different. However, the key issue in the instant case is not the differences of the eukaryotic and prokaryotic expression, the issue here is whether the two carriers, i.e. the plasmid and the recombinant Gram-positive bacterium transformed by a plasmid are functionally equivalent in presenting antigen to the immune system of an eukaryotic animal. This issue has been addressed by the prior art teaching such as *Pouwels et al and Madagnili et al*, where the bacterium was used as a replacement for DNA vaccination carried by a eukaryotic expression vector, and the prior art of record do not demonstrate that using the bacteria carrier system has changed the nature of the

immune response. To the contrary, the use of the bacteria combined with a high efficiency prokaryotic vector has enhanced a heterologous antigen-specific immune response (§ 7.1 of *Pouwels et al*). Apparently, the difference in eukaryotic and prokaryotic expression systems has not affected the efficiency of antigen-presentation, nor the induction nor the nature of an expected immune response to an antigen.

It is noted that it is inaccurate to conclude that *Medaglini* method is "to mimic a pathogen invading the mucosa" (the Declaration, first line of page 6). *Medaglini et al* clearly teach a broader use of the commensal bacteria as a carrier for surface expressing any recombinant protein for inducing an immune response, and illustrated the principle by engineering the *S. gordonii* expressing an *allergen*.

Allergies and Mucosal Immune Response

Applicants then argue that the U.S. 5,958,891 patent teaches expressing allergen in eukaryotic cells, enhanced IFN-γ production related to CD8+ cells; whereas Medaglini method is to elicit an enhanced immunoglobulin response against pathogens, does not teach or suggest suppression of IgE production.

The arguments have been fully considered, but they are not persuasive. As an initiation matter, the original rejection has been modified, particularly it included the teaching of *Janeway Jr.* with respect to shifting the antibody response away from one dominated by IgE toward one dominated by IgG via escalating doses of allergen or inducing T cell anergy. Thus, it is clear that it was known in the art at the time of instant

invention, enhancing an IgG production is not conflicting with suppressing of IgE production, rather, it is a regulatory mechanism for treating allergy.

Applicants then argue that Medaglini discuss pathogen induced immune response, not allergy. While this is true, the discussion of *Medaglini* does not excluding the use of the system for delivering an allergen. This is because *Medaglini et al* clearly acknowledged that the system could be used for broad range of antigens, not limiting to a particular type, and illustrated with an allergen; needless to say it is commonly known in immunology and evidenced by the teaching of *Janeway Jr.* that it is the type of the antigen and routes of administration that determines the type of immune response induced (producing IgG or IgE). *Janeway, Jr.* teaches, "THERE ARE CERTAIN ANTIGENS AND ROUTES OF ANTIGEN PRESENTATION TO THE IMMUNE SYSTEM THAT FAVOR THE PRODUCTION OF IGE" (12-1), "TH2 CELLS CAN SWITCH THE ANTIBODY ISOTYPE FROM IGM TO IGE, OR THEY CAN CAUSE SWICHING TO IGG2 AND IGG4 (HUMAN) OR IGG1 AND IGG3 (MOUSE). ANTIGENS THAT SELECTIVELY EVOKE TH2 CELLS THAT DRIVE AN IGE RESPONSE ARE KNOWN AS ALLERGENS". Therefore, it is well known in the art, that the types of antibodies could switch depending on the antigen given and T cell type activated. Therefore, it is not surprise that even though *Medeglini et al* teach a method of inducing IgG dominated response, the means could be and desirable for the purpose of suppressing IgE production, because it shifts the antibody response away from an IgE-dominated response. Here, LAB is not only a nucleic acid carrier for antigen presentation, but also an adjuvant for the switch of Th1 and Th2 type of immune responses induced. Additionally, the '891 patent teaches that the

suppression of IgE coincides the production of IgG (e.g. fig. 1). Accordingly, the motivation of combining reference is multitude, rather than lacking.

In section 17 of the Declaration, Applicant misinterpreted the Office action by saying "the alleged motivation is that the Gram-positive commensal bacteria of Medaglini could be used to transfer nucleic acid from the bacterium into a eukaryotic cell". However, the Office never attempted to suggest any mechanism with respect to how the bacteria or plasmid works *in vivo*, and how the antigen is presented by the two different systems, these appear to be basic scientific issues that need to be further addressed by the skilled in the art as evidenced by the teaching of *Pouwels et al* (last section of the article) and *Janeway Jr.* (§ 12-15) The duty of the Office is to interpret the claims given the broadest and reasonable interpretation that is consistent with the specification. The original claims read on delivery a nucleic acid using any promoter encompassing eukayotic and prokaryotic promoters, thus, the mode of operation of nucleic acids carried by the bacteria may be different. With the amendment of the claims, these issues have rendered moot.

With respect to the expectation of success, it is noted that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See *In re O'Farrell*, 7 USPQ2d 1673 (CAFC 1988).

Conclusion

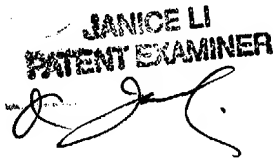
No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942 (571-272-0730, after the Office relocation in January, 2004). The examiner can normally be reached on 9:30 am - 6 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



Q. Janice Li
Patent Examiner
Art Unit 1632

QL
December 12, 2003